The Window of Epileptogenesis: Looking Beyond the Latent Period

Development of Spontaneous Recurrent Seizures after Kainate-Induced Status Epilepticus. Williams PA, White AM, Clark S, Ferraro DJ, Swiercz W, Staley KJ, Dudek FE. *J Neurosci* 2009;29:2103–2112. Acquired epilepsy (i.e., after an insult to the brain) is often considered to be a progressive disorder, and the nature of this hypothetical progression remains controversial. Antiepileptic drug treatment necessarily confounds analyses of progressive changes in human patients with acquired epilepsy. Here, we describe experiments testing the hypothesis that development of acquired epilepsy begins as a continuous process of increased seizure frequency (i.e., proportional to probability of a spontaneous seizure) that ultimately plateaus. Using nearly continuous surface cortical and bilateral hippocampal recordings with radiotelemetry and semiautomated seizure detection, the frequency of electrographically recorded seizures (both convulsive and nonconvulsive) was analyzed quantitatively for 100 d after kainate-induced status epilepticus in adult rats. The frequency of spontaneous recurrent seizures was not a step function of time (as implied by the "latent period"); rather, seizure frequency increased as a sigmoid function of time. The distribution of interseizure intervals was nonrandom, suggesting that seizure clusters (i.e., short interseizure intervals) obscured the early stages of progression, and may have contributed to the increase in seizure frequency. These data suggest that (1) the latent period is the first of many long interseizure intervals and a poor measure of the time frame of epileptogenesis, (2) epileptogenesis is a continuous process that extends much beyond the first spontaneous recurrent seizure, (3) uneven seizure clustering contributes to the variability in occurrence of epileptic seizures, and (4) the window for antiepileptogenic therapies aimed at suppressing acquired epilepsy probably extends well past the first clinical seizure.

COMMENTARY

With most types of acquired epilepsy, an initial precipitating injury to the brain, such as head trauma, stroke, or an episode of status epilepticus, is the cause of the subsequent development of spontaneous, recurrent seizures. The interval between the original brain insult and the clinical presentation of the first seizure is commonly referred to as the latent period of epileptogenesis, which can often span months to years. During this latent period, the process of epileptogenesis occurs, as defined by abnormal changes in the molecular, cellular, and network properties of the brain that develop in response to the injury and ultimately are responsible for producing an epileptic state. From a therapeutic standpoint, while current seizure medications only act to suppress seizures symptomatically, this latent period offers a window of opportunity for initiating potential antiepileptogenic therapies in an attempt to prevent epilepsy from developing in the first place. While many assumptions have been made about the biological mechanisms and clinical implications of epileptogenesis during the latent period, recent work suggests that the conventional concept of the latent period of epileptogenesis may need to be revised.

In the traditional theory, the biological processes mediating epileptogenesis are completed exclusively during the latent period, such that the first seizure heralds an abrupt, step-like transition to a fully mature, stable epileptic state. In this scenario, although seizure frequency might fluctuate in a random fashion, there would be no evidence of systematic or progressive worsening of seizures following the initial presentation of epilepsy. Furthermore, from a therapeutic standpoint, antiepileptogenic therapies would not be predicted to be beneficial, if initiated after the first seizure. An alternative theory postulates that epileptogenesis represents a more gradual, progressive development that extends beyond the latent period. Thus, seizures would be expected to become increasingly more frequent or severe, as a reflection of the underlying epileptogenic events. In the extreme, most controversial version of this viewpoint, seizures themselves may directly cause or contribute to further advancement of the epileptic process (i.e., seizures beget seizures). If the progression of seizures does continue beyond the latent period, then initiation of antiepileptogenic therapies could potentially benefit patients even after the initial clinical seizures.

While many types of epilepsy, such as idiopathic childhood absence epilepsy, typically show no signs of progression and often remit spontaneously, some acquired epilepsies, such as temporal lobe epilepsy associated with mesial temporal sclerosis, can exhibit progressive increases in seizure frequency or severity over time. However, objective documentation of seizure progression in human epilepsy is difficult and controversial, because it is complicated by a number of confounding factors, such as inaccurate seizure histories, the lack of long-term EEG data, and the use of antiepileptic drugs (1,2). Thus, animal models of epilepsy may prove useful in more accurately measuring the duration of the latent period and identifying evidence of systematic changes in seizure properties that reflect an underlying progression of epileptogenesis.

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The recent study by Williams et al. constructs a comprehensive, quantitative analysis of the latent period and the subsequent evolution of seizures using a popular rodent model of temporal lobe epilepsy triggered by an initial episode of status epilepticus. A series of low doses of kainate was administered to rats to induce repetitive convulsive seizures over at least 3 hours. The rats then received almost continuous video-EEG monitoring with radiotelemetry (typically for a minimum of 100 days after kainate injection) to identify the subsequent onset and progression of both nonconvulsive and convulsive spontaneous seizures. In all but one animal, nonconvulsive electrographic seizures first emerged within a median latency of 8 days following kainate administration and preceded the onset of convulsive seizures by about 1 week, indicating that a progression in seizure severity occurs following epileptogenesis in the kainate model. Furthermore, after the onset of the first seizure, there was a nonlinear, progressive increase in seizure frequency. Statistical fitting of the mean daily seizure frequencies from all rats over time revealed a sigmoid shaped curve, involving four stages: 1) an initial phase of no seizures (the latent period), 2) a second phase with a gradual increase in seizure frequency, during which the interseizure intervals were extremely variable and could be nearly as long as the latent period itself, 3) a third stage with an exponential increase in seizure frequency, and 4) a final plateau phase, in which seizure frequency stabilized at a maximal rate. In addition to these stereotypical changes in seizure frequency over time, there was evidence of nonrandom clustering of seizures that was superimposed upon and could mask the underlying increase in seizure frequency in individual animals. Overall, the main conclusion drawn from this study was that epileptogenesis does not represent a stepwise, absolute transition that culminates in the first seizure, but rather reflects a gradually progressive process that continues well beyond the latent period. Furthermore, the data suggest that the latent period and initial evolution of seizure frequency represent probabilistic functions, with the tendency for seizures to occur increasing slowly over time following a brain injury, as the underlying mechanisms of epileptogenesis mature.

This study provides solid evidence to challenge the traditional concept of the latent period of epileptogenesis; however, the findings are not entirely novel. A previous study documented increasing seizure frequency in the kainate model (3), although this finding was based on intermittent behavioral observations only and did not use uninterrupted video-EEG, as employed in the study by Williams and colleagues. Continuous video-EEG monitoring also has been used in a model of electrical stimulation-induced status epilepticus; these studies similarly found that the frequency of spontaneous seizures exhibited an initial increase and reached a plateau over time (4,5).

The progression of seizure frequency documented in the present and previous studies has a number of mechanistic implications. Although the Williams et al. study did not investigate the underlying biological mechanisms involved, presumably the observed increase in seizure frequency following the latent period indicates that mechanisms of epileptogenesis continue to be active after the first seizure occurs. A previous study was able to correlate progressive increases in seizure frequency with loss of hilar interneurons and severe mossy fiber sprouting in the dentate gyrus (5). However, the findings are simply correlative and do not prove cause and effect. Furthermore, the Williams et al. study and the previous work did not address the long-standing controversy about whether seizures themselves contribute to further progression of epilepsy. Future studies are required to determine the mechanistic basis of progressive epileptogenesis.

The clinical implications for a theory of epileptogenesis that extends beyond the latent period are potentially very significant. Although no proven antiepileptogenic treatments have yet been developed for clinical use, it is usually assumed that any antiepileptogenic treatment must be initiated during the latent period in order to be effective. However, practical issues may make it difficult or undesirable to initiate therapy prior to the onset of epilepsy. Thus, if epileptogenesis does continue beyond the latent period, then antiepileptogenic therapies may still have beneficial effects after presentation of the first seizure and the window of opportunity for initiating antiepileptogenic therapies may be much larger than previously believed.

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